PATENT SPECIFICATION (11) 1 557 163

1 557 163

(21) Application No. 26767/75 (22) Filed 24 June 1975
(23) Complete Specification filed 23 June 1976
(44) Complete Specification published 5 Dec. 1979
(51) INT CL² A61K 5/00 31/54
(52) Index at acceptance
A5B 150 170 190 272 27Y 285 28Y 351 35Y 38Y 390 401 402 40Y 481 48Y 523 52Y 546 54Y 566 56Y 586 58Y 671 67Y 822 823 826 F H M

(19)

(54) DENTAL CARE PREPARATIONS

(71) We, ED. GEISLICH SOHNE A.G. FUR CHEMISCHE INDUSTRIE, a Swiss Body Corporate of Wolhusen, Lucerne, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

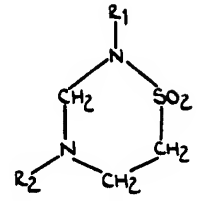
This invention relates to novel preparations for the treatment of tooth and gum infections and in particular parodontosis.

Paradontosis is a progressive, chronic inflammatory infection of the immediate surroundings of the tooth root and the tooth bed (paradontium). This disease, which is increasingly common in men and women over 30 years of age, successively establishes itself in the gingival border, the periodontal membrane and the osseous tooth socket.

A healthy gum lies firmly around the neck of the tooth, but when circulation disorders occur, it becomes flaccid, tends to bleed and loosens itself from the tooth, producing a gingival pocket.

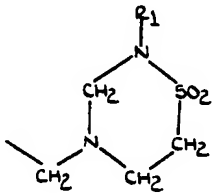
Paradontosis is caused by a bacteria and their metabolic products and it is associated with the build up of tartar and bacterial plaque. We have now found that, although dental care preparations have commonly contained bactericides for many years, without affording significant protection against paradontosis, one particular class of bactericides is very effective. We believe that this effectiveness is due to the unique action of the compounds concerned not only against the bacteria but also against the toxins produced by the bacteria.

The class of bactericides which we have found to be effective against paradontosis are the formaldehyde carriers, that is non-toxic compounds containing formaldehyde in combination, which are capable of producing formaldehyde at the site of action. British Patent Specification No. 1,124,285 discloses and claims one class of such compounds, including *inter alia* compounds of general formula



I

in which R_1 is hydrogen or a straight or branched alkyl group having 1—6 carbon atoms, for example a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, amyl or hexyl group and R_2 is hydrogen or a group of the formula



(wherein R_1 is as defined above).

Thus according to one feature of the present invention there is provided a dental care preparation for the treatment and/or prophylaxis of parodontosis in the form of a toothpaste, toothgel or mouthwash as herein defined comprising, as active ingredient, at least one compound of formula I (as hereinbefore defined).

The expression "toothpaste, toothgel or mouthwash" is used herein to designate preparations of an orally acceptable nature containing carriers and excipients conventionally used for such purposes, with the proviso that it does not include solvents together with the active ingredient of formula I which give rise to more known solutions or suspensions.

We have found, however, that the compound of choice is bis - (1,1 - dioxo - perhydro - 1,2,4 - thiadiazinyl - 4) - methane (also referred to herein as Taurolin) in view of its extremely low toxicity when given over long periods. On the other hand, compounds in which R_1 is alkyl tend to have en-

hanced affinity for the gum which improves their effectiveness.

As indicated, the production of this compound and of the other compounds of formula I is described in British Patent Specification No. 1,124,285.

It is noteworthy that the formaldehyde carriers of formula I are effective in treatment of paradontosis, while chlorhexidine, which has been previously suggested for treatment of parodontosis, is not active against the bacterial toxins and is consequently incapable of complete treatment of the disease. Furthermore, the chlorhexidine digluconate solutions which have previously been used have the disadvantage of causing yellowness of the teeth and further have an unpleasant bitter taste. In addition, chlorhexidine is known to produce p-chloroaniline, a very toxic substance, on degradation, so that it is not suitable for long-term treatment of mouth conditions.

In general, the concentration of the active substance in dental care preparations will be higher in the therapeutic treatment of an established parodontosis than in the prophylactic treatment of the teeth to prevent such disease. For therapeutic purposes, the dental care preparations should contain 1—3% by weight, preferably about 2% by weight, of the active material, while for prophylaxis, the preparations should contain 0.5—1.5% by weight of active material, preferably about 1% by weight.

The dental care preparations into which the active material of formula I will be incorporated are toothpastes, both of the foaming and non-foaming types, tooth gels and mouth washes.

A toothpaste according to the invention may be of conventional composition and may, therefore, contain such ingredients as thickening or binding agents, humectants foaming agents, cleansing agents, preservatives, sweetening agents, flavouring agents and/or water.

Thickening or binding agents will in general be hydrophilic colloids of relatively high viscosity so as to give a creamy consistency to the paste and may, for example, be substances such as carboxymethylcellulose, methylcellulose, alginates, caragheenins, hydroxyethylcellulose, polyvinylpyrrolidone or silicic acid. In general, the quantity of binding or thickening agents will be widely variable, according to the nature of the other components and may vary from 1% up to 30% by weight or more.

Humectants may be such compounds as glycerol, sorbitol or propylene glycol; these substances may constitute a relatively large proportion of the composition, for example 10—30% by weight.

Preservatives which may be present include such substances as hydroxybenzoic acid esters. Sweetening agents include such substances as saccharine or sodium cyclamate. Flavouring agents include various aromatic oils, for example the traditional mint flavour oils.

The cleansing agent will, in general, be a very fine crystalline powder capable of producing light abrasion. The most suitable substance is calcium phosphate dihydrate, but other substances may be used including calcium carbonate, calcium pyrophosphate, aluminium hydroxide, aluminium oxide, calcium lactate, magnesium oxide, magnesium carbonate and precipitated silica.

In general, a relatively small quantity of surface active material will be present to assist cleansing of the teeth, even when the toothpaste is not intended to foam. A wide variety of surfactants are available. One particularly suitable class are polyoxyethylene derivatives of sugar alcohol mono-esters, such as polyoxyethylene sorbitan monolaurate and monostearate. Another product of this type is the polyoxyethylene derivative of castor oil sold under the trade name "Cremophor" EL (registered Trade Mark). It will be appreciated, however, that a very wide range of similar materials may be selected from the conventional surfactants available. In general, a non-ionic surfactant is preferred. In non-foaming preparations, the quantity of such non-ionic surfactants will be of the order of 0.5—1.5% by weight.

Where a foaming toothpaste is required, it is preferred to incorporate an anionic surfactant, such as a long-chain sulphate or sulphonate salt, for example sodium lauryl sulphate. These substances may, for example, be present at a level of 1—3%, e.g. about 2% by weight.

The water present is preferably deionised, to avoid problems in formulation.

It will be appreciated that many variants in the toothpaste formulations according to the invention are possible and the foregoing is not intended as an exhaustive list of the components which are possible.

Tooth gels will, in general, be very closely similar to toothpaste but will lack the abrasive tooth cleaning material and will thus generally be relatively optically clear. A medically exceptable dye will commonly be present in such formulations.

Mouth washes according to the invention may, again, be of the conventional type and may contain, for example, sweetening and flavouring agents, surfactants and/or, commonly, ethanol. Surfactants which may be present include non-ionic surfactants such as the polyoxyethylene derivatives mentioned above in relation to toothpastes, as well as the anionic surfactants also mentioned above. In general, mouth washes will be used therapeutically and will therefore contain the active material at the higher level as mentioned above.

Preparations according to the invention may, if desired, contain at least one further pharmacologically active ingredient such as, for example, a substance active against the formation of bacterial plaque, for example sodium benzoate, high molecular polyphosphates, sodium metaphosphate, magnesium tartrate, polyvinylpyrrolidone, polysiloxanes or sodium sulphoricinoleate. Similarly, preparations may contain substances active against caries, for example fluorine compounds.

The following Examples are given by way of illustration only. In the Examples, all percentages are percentages by weight.

Example 1
Tooth gel

21.0% "Sident" 3 (registered Trade Mark) (Silicic acid: Degussa)
29.0% Glycerine
28.0% Karion F liquid (70% Sorbitol solution. E. Merck, Darmstadt)
13.0% Propylene glycol
3.75% Water (deionised)
0.05% Saccharine (pure)
1.0% Taurolin
0.4% "Tween" 20 (registered Trade Mark) (Polyoxethylen-Sorbitan-monolaurate: Atlas)
0.8% "Tween" 60 (Polyoxethylen-Sorbitan-monostearate: Atlas)
1.0% Oleum menthae
2.0% "Texapon" K12 (registered Trade Mark) (Sodiumlauryl salate: Henkel/Dehydag)

Example 2
Tooth gel, foaming

2.0% "Texapon" K12
1.0% Taurolin
1.5% Natrosol HR 250 (Hydroxylethyl-Cellulose: Hercules Powder)
10.0% Kollidon 30 or 17 (Polyvinyl-pyrrolidone: BASF)
0.5% Carmoisine B (Fast Red E) C.I. 16045 (Red Dye)
82.8% Water (deionised)
0.5% Saccharine 10% Solution
0.8% "Tween" 60
0.4% "Tween" 20
0.5% Oleum menthae

Example 3
Tooth gel, non-foaming

1.0% Taurolin
1.5% Natrosol HR 250
10.0% Kollidon 30 or 17
0.5% Carmoisine B (Fast Red E) C.I. 16045
3.0% "Cremophor" EL (Castor-oil-ethyleneoxide adduct: BASF)
0.5% Oleum menthae
1.0% Ethanol
0.5% Saccharine 10% solution
82.0% Water (deionised)

Example 4
Tooth gel, non-foaming

1.0% "Carbopol" 934 (registered Trade Mark) (Acrylic acid polymer: B. F. Goodrich)
5.0% Kollidon 30 or 17
1.0% Taurolin
0.3% Carmoisine B (Fast Red E) C.I. 16045
90.5% Water (deionised)
0.5% Saccharine 10% solution
0.5% Oleum menthae
0.8% "Tween" 60
0.4% "Tween" 20
pH adjusted to 7 with Triethanolamine.

Example 5
Tooth gel, non-foaming

1.0% "Carbopol" 940
5.0% Kollidon 30 or 17
1.0% Taurolin
0.5% Carmoisine B (Fast Red E) C.I. 16045
88.5% Water (deionised)
0.5% Saccharine 10% solution
0.5% Oleum menthae
3.0% Cremophor EL

Example 6
Tooth gel, non-foaming

1.0% Taurolin
1.5% Natrosol HR 250
10.0% Kollidon 30
0.5% Carmoisine B (Fast Red E) C.I. 16045
0.5% Oleum menthae
2.0% Ethanol
4.0% Saccharine 10% solution
1.0% "Cremophor" EL (Castor-oil with Aethylenoxid-Product: BASF)
79.5% Water (deionised)

Example 7
Tooth gel, non-foaming

1.0% "Carbopol" 941
5.0% Kollidon 30 or 17
1.0% Taurolin
0.5% Carmoisine B (Fast Red E) C.I. 16045
90.3% Water (deionised)
0.5% Oleum menthae
9.8% "Tween" 60
0.4% "Tween" 20
0.5% Saccharine 10% solution

Example 8
Toothpaste, foaming

1.0% "Methocel" 4000 cps. (registered Trade Mark) (Methyl cellulose: Dow Chemical Midland Mich. USA)
1.0% Taurolin
23.05% Water (deionised)
19.0% Propyleneglycol
9.3% Glycerine

0.25% "Nipagin" M* (registered Trade Mark) (Methyl p-hydroxybenzoate: Nipa Laboratories Treforest, Pontypridd)
0.5% Saccharine 10% solution
1.2% Paraffin oil
1.0% Oleum menthae
2.0% "Texapon" K 12
41.7% Calcium phosphate dihydrate

* can be omitted.

Example 9
Toothpaste, foaming

1.0% "Methocel" 4000 cps.
1.0% Taurolin
21.7% Water (deionised)
19.0% Propylene glycol
9.3% Glycerine
0.5% Saccharine 10% solution
1.0% Paraffin oil
1.0% Oleum menthae
2.0% "Texapon" K 12
43.5% Calcium carbonate (precipitated)

Example 10
Toothpaste, foaming

33.0% Calcium carbonate (precipitated)
34.8% Water (deionised)
20.0% Glycerine
3.0% Sorbitol
2.0% "Aerosil" (registered Trade Mark) (Fine silicic acid: Degussa)
2.0% Texapon K 12
1.0% Oleum menthae
1.2% "Texamid" 578 L (registered Trade Mark) (Sodium Alginate: Henkel/Dehydag)
1.0% Paraffin oil per l
1.0% Taurolin
1.0% Saccharine 10% solution

Example 11
Mouth wash

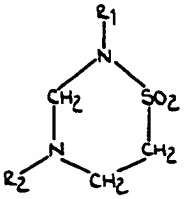
79.0% Water (deionised)
2.0% Haurolin
1.0% "Texapon" K 12
15.0% Ethanol
0.5% Saccharine 10% solution
0.5% Oleum menthae
2.0% "Tween" 80 (Polyoxyethylene-sorbitan-mono-oleate: Atlas)

Example 12
Mouth wash

73.8% Deionised water
2.0% Taurolin
10.0% Ethanol
1.5% Parfum dentifrice 24/45 (Charabot, France)
0.2% Methol crystalline (Charabot, France)
5.0% Tinct. arnica
5.0% Hamaelis Extract
0.5% Kamillen Extract
2.0% "Texapon" K 12

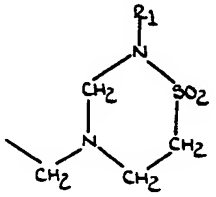
WHAT WE CLAIM IS:—

1. A dental care preparation for the treatment and/or prophylaxis of parodontosis in the form of a toothpaste, toothgel or mouthwash (as herein defined) comprising, as active ingredient, at least one compound of formula



I

[wherein R_1 represents a hydrogen atom or a straight or branched alkyl group having from one to 6 carbon atoms; and R_2 represents a hydrogen atom or a group of formula



(wherein R_1 is as defined above)].

2. A preparation as claimed in claim 1 wherein the active ingredient is bis - (1,1 - dioxo - perhydro - 1,2,4 - thiadiazinyl - 4) - methane.

3. A preparation as claimed in either of claims 1 and 2 in the form of a toothpaste or toothgel containing thickening or binding agents, humectants, foaming agents, cleansing agents, preservatives, sweetening agents, flavouring agents and/or water.

4. A preparation as claimed in either of claims 1 and 2 in the form of a mouthwash containing sweetening and flavouring agents, surfactants and/or ethanol.

5. A preparation as claimed in any of the preceding claims containing at least one further pharmacologically active ingredient.

6. A preparation as claimed in claim 5 wherein the further active ingredient is a substance active against the formation of bacterial plaque, or a substance active against caries.

7. A preparation as claimed in claim 6 wherein the substance active against the production of bacterial plaque is sodium benzoate, a high molecular polyphosphate, sodium metaphosphate, magnesium tartrate, polyvinylpyrrolidone, a polysiloxane or sodium sulphoricinoleate.

8. A preparation as claimed in claim 6 wherein the substance active against caries is a fluorine compound.

9. A preparation as claimed in any of the preceding claims for the treatment of parodon-

tosis containing from 1 to 3% by weight of the active ingredient of formula I.

10. A preparation as claimed in claim 9 which contains about 2% by weight of the active ingredient of formula I.

11. A preparation as claimed in any of claims 1 to 8 for the prophylaxis of parodontosis containing from 0.5 to 1.5% by weight of the active ingredient of formula I.

12. A preparation as claimed in claim 11 which contains about 1% by weight of the active ingredient of formula I.

13. A preparation as claimed in claim 1 substantially as herein described.

14. A preparation as claimed in claim 1 substantially as herein described in any of the Examples.

For the Applicants
FRANK B. DEHN & CO.
Chartered Patent Agents
Imperial House,
15—19, Kingsway,
London, W.C.2

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1979
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.